

## EDITORIAL

# Towards early individual goal-directed coagulation management in trauma patients

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Major trauma is associated with significant blood loss due to both the severity of injuries and trauma-related coagulopathy. Acute coagulopathy in trauma patients is frequent and has been associated with a worse clinical outcome.<sup>1 2</sup> In this issue of the *British Journal of Anaesthesia*, Fries and Martini<sup>3</sup> review the mechanisms of trauma-related coagulopathy and the central role of fibrinogen in its treatment. This is a very timely issue since the understanding of the coagulopathy of trauma and shock has indeed increased tremendously in recent years. In addition, fibrinogen is increasingly viewed as the coagulation factor that is the first to become critically low in cases of major haemorrhage.<sup>1</sup>

Acute traumatic coagulopathy has traditionally been explained as an acquired disorder in the coagulation system which occurs through loss or impaired function of coagulation proteases and platelets. However, severe trauma leads to massive haemorrhage with activation and subsequent exhaustion of the coagulation system. Dilution from fluid resuscitation results in an additional relative deficiency of coagulation factors and platelets. Finally, physical factors such as acidaemia and hypothermia further compromise coagulation proteases and platelet function, worsening the evolving coagulopathy.

Recent studies have shown that nearly 25% of trauma patients present with a clinically significant coagulopathy upon arrival in the emergency department which affects their overall outcome.<sup>4</sup> Interestingly, this early coagulopathy occurred before any significant consumption or fluid administration and in the absence of a relevant acidaemia or hypothermia. Therefore, it has been postulated that the

early coagulopathy after trauma be physiologically and mechanically distinct. This acute coagulopathy of trauma, which has also been called endogenous acute coagulopathy<sup>5</sup> or acute coagulopathy of trauma and shock,<sup>6</sup> is driven by a combination of tissue trauma and shock with systemic hypoperfusion. Thus, the anticoagulant thrombomodulin protein C pathway is overtly activated, resulting in reduced pro-coagulatory potential and increased fibrinolytic activity.<sup>7 8</sup> Once protein C is activated through a thrombin-thrombomodulin-dependent reaction, activated protein C (aPC) exerts its profound anticoagulant effects by irreversibly inactivating factors Va and VIIIa. In addition to its direct inhibition of fibrin formation, aPC causes resolution of formed clots by stopping the inhibition of fibrinolysis by direct inhibition of plasminogen activator inhibitor 1.<sup>9 10</sup>

After major trauma, surgeons and anaesthetists are faced with a dual problem of physical damage, including vascular injury, with 'surgical' haemorrhage and a component of coagulopathy with 'coagulopathic' bleeding (and any combination thereof). The first requires surgical control, and the second requires treatment with pro-coagulatory substances such as labile/allogeneic blood products, coagulation factor concentrate, and, potentially, anti-fibrinolytics. In this situation, the physician must first immediately analyse the situation to establish whether coagulopathy is present and subsequently decide what should be used for treatment, given the hazards, unknowns, and costs of allogeneic blood products, factor concentrates, and anti-fibrinolytics.

A first option to boost blood coagulation after major trauma is to administer a 'massive transfusion package' with a fixed

ratio of fresh frozen plasma (FFP) to red blood cell (RBC), some with a high ratio and some even include platelets.<sup>11</sup> The apparent success of such algorithms in improving survival of US Army combat victims has been described.<sup>1 12</sup> However, there are also studies, in which a high FFP:RBC regimen has shown no benefit with regards to survival.<sup>13 14</sup> There is an important study showing that the introduction of 'massive transfusion packages' resulted in a significant reduction in mortality without a change in the FFP:RBC ratio given in the first 24 h.<sup>15</sup> Interestingly, in this study, FFP (169 vs 254 min) and platelets (241 vs 418 min) were administered much earlier after the introduction of 'massive transfusion packages'.<sup>15</sup> There are several important aspects to consider when interpreting results of studies showing a benefit of a high FFP:RBC ratio in trauma patients. The data are retrospective and primarily refer to young, previously healthy male patients with penetrating injuries. In addition, the FFP:RBC ratio usually is calculated for the first 24 h of treatment. Therefore, there may be a significant selection bias in that clinicians may have allocated most resources, including FFP, to those patients most likely to survive.<sup>16</sup> There may also be a survivor bias in that those with the worst injury and bleeding died too early to receive a large amount of FFP.<sup>16 17</sup> In addition, FFP transfusion is associated with adverse effects such as increased incidence of nosocomial infections,<sup>18</sup> multiple organ failure,<sup>17</sup> lung injury,<sup>16 17</sup> and possibly mortality.<sup>16 19</sup> Therefore, although the use of FFP is suggested in massive bleeding, the recently published AABB guidelines<sup>12</sup> and the updated European guideline on the management of bleeding after major trauma<sup>1</sup> do not recommend transfusion of plasma at a FFP:RBC ratio of 1:3 or more.

A second treatment option aimed at early, individual optimization of blood coagulation after major trauma is to assess each trauma patient's coagulation status on admission in the emergency room and throughout the surgery with point-of-care viscoelastic coagulation monitoring (thrombelastography, TEG®, Haemonetics Corp., formerly Haemoscope or rotational thromboelastometry, ROTEM®, tem innovations GmbH, formerly Pentapharm).<sup>20 21</sup> These bed-side devices allow analysis of the entire blood coagulation within 10–15 min<sup>22</sup> including the detection of (hyper)fibrinolysis.<sup>7 8</sup> With this information, coagulation can be readily and individually optimized, for example, with anti-fibrinolytics and blood coagulation factor concentrates and later, if necessary with labile blood products. With such an algorithm, the use of RBC, FFP, and platelets can be significantly reduced<sup>23</sup> and survival of trauma patients may be significantly improved.<sup>24</sup> In this study, the observed mortality was 24.4% which was significantly lower than the expected mortality based on the trauma injury severity score (TRISS) of 33.7%.<sup>24</sup>

Fibrinogen may be the key element of blood coagulation and is the first element to get critically low.<sup>1</sup> Fibrin polymerization can be compromised by colloids which are frequently used in the initial resuscitation of trauma victims. Interestingly, this form of blood coagulation compromise can be reversed by the administration of fibrinogen.<sup>25</sup> Therefore, aiming at functional fibrinogen levels as assessed by

thromboelastometry<sup>23 24</sup> appears reasonable. This is also proposed in the updated European guidelines on the management of bleeding after major trauma.<sup>1</sup> If thrombelastometric monitoring is not available, serum fibrinogen levels of 1.5–2.0 g litre<sup>-1</sup> should be targeted.<sup>1</sup> However, clinicians should be aware that in the presence of artificial colloids such as hydroxyethyl starch, gelatin, or dextran, the most often used fibrinogen measurement method, the Clauss method, significantly overestimates fibrinogen concentration.<sup>26 27</sup>

An additional benefit of bed-side coagulation monitoring is speed. If the coagulation status measured on arrival in the emergency department, the main coagulation problem is known within 15 min. The trauma patient can then immediately and specifically be treated according to an institutional transfusion algorithm. Importantly, guidelines aimed at optimizing the individual's coagulation status also avoid excessive pro-coagulatory potential with associated thrombotic complications. The time advantage of bed-side coagulation monitoring compares very favourably with the improved times of FFP administration described in the study of the introduction of a massive transfusion package.<sup>15</sup>

The review by Fries and Martini<sup>3</sup> explaining the mechanisms of coagulopathy of trauma and shock and the central role of fibrinogen is an important contribution towards a better understanding of this complex situation and a better treatment of trauma patients. Their recommendation to view fibrinogen as a central element of blood coagulation is in agreement with the updated European guideline on the management of bleeding after major trauma.<sup>1</sup> The first goal is that all hospitals treating trauma patients have an institutional algorithm for the management of a trauma patient with major bleeding. The ultimate goal is to establish algorithms allowing early individual goal-directed coagulation management in trauma patients. To introduce such concepts into general medicine, they need to be rigorously tested in large prospective randomized trials.

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